Amendments to the Claims are reflected in the listing of claims which begins on page 22 of this paper.

There are no Amendments to the Drawings.

Remarks/Arguments begin on page 25 of this paper.

A clean copy of the specification as amended without editorial marks appears at Tab A.

A clean copy of the new claim appears at Tab B.

Amendments to the Specification:

The heretofore unamended specification has now been extensively amended primarily by deletions, rearrangement of sentences and clarification of disclosed terms. Accordingly, a complete copy of the marked-up specification follows. A clean copy of the specification as amended now appears at Tab A.

~~BOWEL CLEANSING COMPOSITION~~

A METHOD FOR CLEANING THE COLON FOR EXAMINATION

[0001] The instant application is a continuation-in-part of co-pending U.S. patent application Serial No. 10/194,251, filed July 15, 2002.

BACKGROUND OF THE INVENTION

[0002] The invention relates to ~~compositions~~ a method for rapid bowel cleansing which ~~are~~ is particularly useful for ~~preparing~~ removing fecal matter from the bowel prior to surgery or a diagnostic ~~procedures~~ procedure such as a ~~colonoscopies~~ colonoscopy.

~~1.~~ FIELD OF THE INVENTION ~~of the Invention~~

~~Gastrointestinal agents for regulating bowel movement can conveniently be placed into two categories: laxatives and bowel cleansers. Laxatives are formulated for long-term use, with the intention of eliminating constipation and obtaining a regular bowel function. Many laxatives work by stimulating bowel motility (peristalsis) in various~~

~~ways, as by distending the gut with bulking or osmotic agents, or by directly stimulating the bowel nerves or muscles with stimulant laxatives. Other laxatives function as stool softeners or lubricants. The various types of laxatives are often combined in attempts to maximize efficacy or to reduce side effects of the agents.~~

[0003] Bowel cleansers, also called purgatives, cathartics, and lavages, are formulated for rapid emptying of the bowel and are intended for short-term use only. They are commonly used as "bowel preps" for emptying the bowel prior to surgery, childbirth, or diagnostic procedures, and usually comprise an osmotic or stimulant ~~laxative~~ administered by either oral or anal route. While purgatives formulated for patient use as enemas are often prescribed before examinations, ~~they are~~ purgatives are awkward to handle and are frequently not properly administered, so orally-administered preparations are generally preferred for emptying the bowel. However, the orally-administered compositions for rapid bowel cleansing in common use also have disadvantages which discourage patient compliance. Such disadvantages include an unpleasant taste, a requirement to drink a lot of fluid with the orally-administered composition, bloating and nausea.

~~2. DESCRIPTION OF RELATED ART~~

[0004] The most commonly prescribed prior art oral bowel preps ~~today~~ for bowel examination ~~comprise~~ include sodium phosphate compositions in varying proportions of mono- and dibasic species, and polyethylene glycol (PEG) in combination with electrolytes.

[0005] Sodium phosphate is a saline osmotic laxative, sold, for example, as Fleet Phospho-Soda® (C.B. Fleet Co., Lynchburg, Virginia), which contains both monobasic and dibasic uncoated sodium phosphate powders. ~~It~~ Sodium phosphate is also sold as Visicol™, which ~~comprises~~ includes ~~mono-~~ monobasic and dibasic sodium phosphates in tablet form. This laxative, when formulated and used as a bowel cleanser, is associated with nausea, vomiting, and symptoms of electrolyte imbalance[[;]]. ~~the~~ The product also has an unpleasant taste. As a result, patient compliance is difficult to obtain, particularly when the bowel cleanser is supplemented with, for example, another saline agent such as a magnesium salt, or a bowel stimulant such as bisacodyl.

[0006] While PEG is known for its successful use as a long-term osmotic laxative in combination with dietary fiber (as described in U.S. Patent 5,710,183, issued January 20, 1998 to Halow, and incorporated herein by reference), PEG purgatives such as Colyte® (Braintree Laboratories, Braintree, MA) have poor patient compliance. They have an unpleasant taste, and the amount and frequency of fluid the ~~patent~~ patient is required to drink, typically 8 fluid ounces every ten minutes over several hours, frequently ~~cause~~ causes severe bloating and attendant nausea. Further, although these prior art purgatives normally include electrolytes to counterbalance electrolyte loss during treatment, symptoms of electrolyte imbalance are, notwithstanding, often experienced by the patient.

SUMMARY ~~OF THE DISCLOSURE~~

[0007] The ~~inventions~~ invention disclosed herein is a method for obtaining a clean colon suitable for visual examination during colonoscopy ~~accordingly provide dry bowel cleansing compositions for oral administration comprising~~ through the use of ~~polyethylene glycol~~ disodium phosphate to initiate the flow of diarrhea~~; dibasic sodium phosphate~~ and polyethylene glycol to maintain the flow of diarrhea~~; and, optionally, monobasic sodium phosphate; which~~. The two ingredients are provided to the patient in powdered form, then dissolved by the patient in water ~~an aqueous carrier~~ prior to use. ~~For added potency in certain clinical applications a bowel stimulant such as biscodyl, or other agent known for its laxative properties may be taken in conjunction with the administration of these compositions as appropriate.~~

[0008] The ~~inventions further provide methods~~ disclosed method provides for the short-term use of the disclosed composition ~~compositions~~ as ~~cathartics~~ a cathartic in ~~emergency situations or in severe constipation, or as~~ bowel ~~preparations~~ preparation prior to surgery, prior to bowel examinations, prior to childbirth, or prior to similar ~~occasions~~ situations necessitating a bowel without fecal matter contained therein.

[0009] The ~~compositions~~ disclosed method for obtaining a clean colon ~~without~~ free of fecal matter ~~contained therein~~ demonstrates ~~demonstrate~~ significantly improved patient compliance and very good efficacy. Patients who ingested the composition reported no bloating or nausea, nor any complaints about the taste.

[0010] Because of the relatively low volume of liquid to be ingested and relatively fast action of the method disclosed herein, use of the disclosed method

provides a clean colon suitable for examination without inducing an osmotic imbalance in the colon. Therefore, it is not necessary to use additional electrolytes along with the PEG/sodium phosphate solution to prevent an osmotic imbalance in the colon.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIGURES 1-6 are ~~still~~ photographs extracted from a video taken during a colonoscopy of six different patients~~, illustrating~~ that illustrate the clean-out of various sections of ~~their colons~~ the colon using ~~a bowel prep according to~~ the ~~invention~~ disclosed method.

DETAILED DESCRIPTION OF THE ~~INVENTION~~ EMBODIMENTS

~~Polyethylene glycols useful in the composition of the invention broadly comprise any food-grade or pharmaceutical-grade PEG. Currently preferred for convenience of use in preparing and using the composition of the invention are polymers having molecular weights above about 900 which are solid at room temperature and soluble in or miscible with water. Polymers having average molecular weights between about 3000 and 8000 are exemplary; PEG 4000, which is nearly odorless and tasteless and widely available in USP grade, or PEG 3350, are very suitable. A proprietary laxative, MiraLax® (Braintree Laboratories, *supra*), is a useful source of PEG 3350 powder readily soluble in water. Other suitable PEG powders are commercially available, as from the Spectrum Chemical Mfg. Company, Gardena, CA. Non-powdered PEG should be comminuted to a particle size that is readily soluble in water before use.~~

[0012] Use of disodium phosphate powder in the disclosed method complements the effect of the PEG component in the dissolved composition. Disodium phosphate is used in amounts to provide the desired osmolarity for initially stimulating diarrhea. The PEG component of the composition maintains the bowel hypermotility induced by the disodium phosphate for a longer period of time, thereby assuring a clean colon for examination.

[0013] The sodium phosphate powder component, according to the ~~invention~~ disclosed method, ~~comprises a~~ includes any pharmaceutical-grade (USP) free flowing powder of anhydrous dibasic sodium phosphate ($Na_2,HPO_4,$, disodium phosphate), optionally in combination with monobasic sodium phosphate monohydrate ($Na_2HPO_4 \cdot H_2O$, monosodium phosphate). ~~, or anhydrous, such as conventionally used in saline laxatives, for example, the powders described in the Fleet Phospho-Soda® composition discussed supra.~~ The disclosed disodium phosphate powder provides ~~the composition of the invention with~~ a saline osmotic effect ~~which complements the effect of the PEG component and is used in amounts which provide the desired osmolarity for this purpose, as known in the art.~~ to initially stimulate short-term hypermotility of the intestines and cause fecal matter to move through the bowels. The sodium phosphate powder should be readily soluble in an aqueous drink medium to promote optimum palatability and patient compliance. Reduced-solubility sodium phosphate powders, such as those powders coated with insoluble materials, are not recommended for use in the disclosed composition.

[0014] The polyethylene glycol component broadly comprises any food-grade or pharmaceutical-grade PEG. Conveniently used PEG polymers in the composition have molecular weights between about 3000 Daltons and 8000 Daltons. Odorless and tasteless PEG polymers that are widely available and suitable for use in the disclosed method include PEG 4000 and PEG 3350. For example, Braintree Laboratories's MiraLax® is a useful source of water soluable PEG 3350 powder, along with PEG powders from Spectrum Chemical Mfg. Company in Gardena, CA. If non-powdered PEG is used, it should be comminuted to a particle size that is water soluble before use.

[0015] In another embodiment of the method of the invention, lower molecular weight PEG powders, such as PEG 400, are used in the composition in lieu of the higher molecular weight PEG powders discussed above. These lower weight polymers may be used if liquid at room temperature and in the same proportion by weight when the sodium phosphate powder is mixed in. If desired, the solution of liquid PEG and sodium phosphate powder may then be diluted to taste with an aqueous liquid.

[0016] To ~~administer,~~ enable the step of administering the disodium phosphate and PEG powders to the patient in the preferred embodiment, the combination of the sodium phosphate powder and the PEG powders powder ~~are~~ is simply dissolved by mixing them into any desired aqueous carrier, such as water ~~or~~ ~~juice~~ or other clear liquid. The two powders are combined in amounts to first stimulate

hypermotility in the bowel then maintain this hypermotility. Following consumption of the mixture, the bowels will preferably be evacuated in 3-4 hours.

[0017] ~~PEG and phosphate powder are combined in amounts which provide a composition that will preferably evacuate the bowel in the course of a few (3-4) hours.~~ Satisfactory bowel evacuations occur using different amounts of each type of powder in combination. It has been found that ~~Compositions~~ compositions ranging from at least about 50% to about 90% by weight of PEG powder, and from at least about 10% to about 50% by weight of sodium phosphate powder, based on the combined weight of the sodium phosphate powder and the PEG ~~in the composition, are provided~~ powder combination provide satisfactory results. Typically, a dry ~~prep~~ bowel examination preparation composition for use in the disclosed method ~~according to the invention~~ will contain about 60 to about 80% by weight of PEG powder and about 20 to about 40% by weight of sodium phosphate powder [[;]]. ~~the term "phosphate" herein refers to either disodium phosphate alone, or disodium phosphate in combination with monosodium phosphate. In typical embodiments, the amount of PEG in a composition according to the invention will be about 70 to 80% by weight, and 20 to 30% by weight sodium phosphate, based on the total amount of PEG and phosphate; the combined PEG and phosphate should make up no less than about 80% by weight of a composition containing additives for optimum results. Compositions containing about 75 to 80% by weight PEG and 20 to 25% by weight phosphate are particularly contemplated for most applications. However, under some circumstances it may be desirable to use amounts of PEG at the high end of the range (e.g., from above about 80% to about 90% by~~

~~weight) with a concomitant decrease of phosphate to below about 20% by weight to about 10% by weight, for example to obtain a more rapid bowel cleanout. Conversely, under some circumstances, amounts of phosphate at the high end of the range (e.g., from above about 40% to about 50% by weight) with a decrease in PEG to below about 60% to about 50% by weight may be desirable. Generally, at least a major amount (greater than about 50% by weight) of the phosphate present is disodium phosphate; if monosodium phosphate is included in the composition, it should usually make up less than one-half, and preferably less than one-quarter, of the phosphate content of the composition~~

[0018] In another typical implementation of the disclosed method, the amount of PEG powder will be about 70 to about 80% by weight, and about 20 to about 30% by weight sodium phosphate powder, based on the total weight of the combination of PEG powder and sodium phosphate powder. The combined PEG powder and the sodium phosphate powder should make up no less than about 80% by weight of a composition containing additives for optimum results. Use of combinations containing about 75 to about 80% by weight PEG powder and about 20 to about 25% by weight sodium phosphate powder in the disclosed method are preferred for most applications. However, under some circumstances it may be desirable to use amounts of PEG powder at the high end of the range (e.g., from above about 80% to about 90% by weight) with a concomitant decrease of sodium phosphate powder to below about 20% by weight to about 10% by weight, for example to obtain a more rapid bowel cleanout. Conversely, under some circumstances, amounts of sodium phosphate powder at the

high end of the range (e.g., from above about 40% to about 50% by weight) with a decrease in the amount of PEG powder to below about 60% to about 50% by weight may be desirable. Generally, at least a major amount (greater than about 50% by weight) of the sodium phosphate powder present is disodium phosphate. If monosodium phosphate is included with the composition disodium phosphate, the monosodium phosphate should usually make up less than one-half, and preferably less than one-quarter, of the phosphate content of the composition combination of the monosodium phosphate and the disodium phosphate.

[0019] To formulate a convenient single dosage drink for use in the disclosed method, a combination of dry ~~prep composition containing from~~ powders is made which contains about 45 grams to about 130 ~~g~~ grams PEG powder and from about 5 grams to 45 ~~g~~ grams sodium phosphate powder, ~~typically~~ preferably from about 45 grams to about 70 grams powdered PEG and 10 to 30 grams phosphate powder~~, preferably~~. Acceptable results from use of the disclosed method were obtained from use of about 55 grams to about 65 grams PEG and about 15 grams to about 25 grams sodium phosphate powder, ~~is~~ dissolved or suspended in an aqueous liquid of choice, such as water, tea, or juice. ~~The phosphate powders should be readily soluble in the aqueous drink medium to promote optimum palatability and patient compliance. Reduced solubility powders such as powders coated with insoluble materials are not recommended. Suitable powders for use in the practice of the present invention~~ comprise ~~the water soluble free flowing untreated powders described and exemplified *supra* as mono and di sodium phosphate powders commonly used in this art. In an~~

~~exemplary drink formulation, a single dose dry prep composition containing from about 58 to 63 grams PEG and from about 15 to 20 grams phosphate powder, for example, 60 grams powdered PEG and 18 grams sodium phosphate powder, preferably disodium phosphate powder, is dissolved in about 1 to about 1.5 quarts of water or other aqueous liquid, for oral ingestion. Alternatively, the compositions can be dissolved in a smaller portion of water, such as eight fluid ounces, and the remainder of the liquid taken in conjunction with this solution. The amount of water or other aqueous medium in which the dry prep composition is dissolved or which is taken with the dry prep composition is not critical~~; however~~, for optimum bowel cleansing, at least about a pint should be used, and preferably at least a quart, depending upon the patient's total liquid intake during the treatment.~~

[0020] In an exemplary drink formulation, a single dose dry prep composition containing from about 58 grams to about 63 grams PEG powder and from about 15 grams to about 20 grams sodium phosphate powder, for example, about 60 grams powdered PEG powder and about 18 grams sodium phosphate powder, preferably disodium phosphate powder, is dissolved in about 1 quart to about 1.5 quarts of water or other aqueous liquid, for oral ingestion. Alternatively, the combination of PEG powder and sodium phosphate powder can be dissolved in a smaller portion of water, such as about eight fluid ounces. The remainder of the about 1 quart to about 1.5 quarts of water is then taken in conjunction with this solution of the powders and the about eight fluid ounces of water. The amount of water or other aqueous medium in which the combination of the PEG powder and the sodium phosphate powder is

dissolved or which is taken with the combination of the PEG powder and the sodium phosphate powder is not critical. However, for optimum bowel cleansing, at least about a pint of water or other aqueous medium should be used, and preferably at least a quart of water or other aqueous medium, depending upon the patient's total liquid intake during the execution of the disclosed method.

~~In another embodiment of the invention, lower molecular weight PEG polymers such as PEG 400 which are liquid at room temperature may be used in in lieu of the above powdered PEG polymers in the same proportion by weight, and the phosphate powder dissolved therein; if desired, the solution may then be diluted to taste with an aqueous liquid. Also, a solution of the phosphate powder may be combined with the liquid PEG instead of the powder, *per se*.~~

[0021] The single dosage drinks ~~so prepared~~ including the PEG/sodium phosphate combination used in the disclosed method are taken from twice per day to four times per day on the day preceding the colonoscopy or other procedure, depending upon the degree of bowel clean-out required and the presence of any complicating bowel conditions ~~such as constipation~~. Typically, in an average patient, a method including the administration of two single dosage drinks twice per day for one day will provide the desired ~~result~~ level of bowel clean-out. ~~If, for example, the patient has failed a standard prep, a two day prep is recommended. Preferably, the patient is restricted to a clear liquid diet while on the regimen, *i.e.*, a diet of liquids containing no significant solid material. Suitable clear liquids include apple juice, tea, plain Jello®, 7-Up®, Sprite®,~~

~~and chicken or beef broth. If the patient receives a sufficient amount of liquids containing sodium and potassium ions to satisfy hunger, no supplemental electrolytes need be used with the PEG/ phosphate compositions.~~

[0022] If the patient has not obtained satisfactory results with a prior bowel clean-out method, it is recommended to use of the disclosed method for two days, along with a clear liquid diet with sufficient sodium and potassium ions. A suitable clear liquid diet contains no significant solid material. Suitable clear liquids for a clear liquid diet include apple juice, tea, plain Jello®, 7-Up®, Sprite®, and chicken or beef broth. If the patient receives a sufficient amount of liquids that contain sodium and potassium ions to satisfy hunger, correct any osmotic imbalance, and prevent obscuring any pathological features present in the colon, no supplemental electrolytes need be used with the disclosed PEG/sodium phosphate combination.

~~For added potency in certain clinical applications, the compositions may be taken in conjunction with a bowel stimulant such as bisacodyl, generally available over the counter as Dulcolax®, BiscoLax®, or other proprietary product. For use with the present invention, bisacodyl should not be taken in powder form to avoid neutralization with stomach acids. Enterin-coated 10 milligram tablets once or twice a day are suitable.~~

[0023] ~~The compositions may include, or be taken in conjunction with, conventional additives such as flavoring or coloring agents. While not presently recommended, an herbal bowel stimulant such as Cascara sagrada may also be included in or taken in conjunction with the inventive compositions~~. To improve

palatability of the disclosed combination, flavoring or coloring agents may be added to the dissolved sodium phosphate and PEG powders. Kits containing single dosage drinks may include optional adjuvants, such as flavor packets, dietary powders, such as powdered bouillon, or herbal preparations. Additionally, stool-bulking agents, including psyllium or other fiber products commonly used as a stool-bulking agent, may be ~~optionally~~ added to or taken with the ~~compositions, both for its laxative properties and its potential ability to~~ PEG/sodium phosphate combination. Added bulking agents may counteract any adverse effects of the other components of the PEG/sodium phosphate combination. ~~Kits containing single dosage units with optional adjuvants such as flavor packets, dietary powers such as powdered bouillon, or herbal preparations are also provided.~~

EXAMPLES

METHODS AND MATERIALS:

[0024] Patients were ~~prepared~~ asked to prepare for a colonoscopy ~~with a dry prep composition of~~ by ingesting about 60 grams PEG powder and about 18 grams ~~disodium~~ of a sodium phosphate powder ~~per dose~~ including all disodium phosphate. Each patent was given two single-dose packets of the described combination for self-administration on the day preceding the colonscopy, with instructions to dissolve each single dose packet in water and then drink the first dose at 10 a.m. and drink the second dose at 4 p.m. For each patient, a clear liquid diet was prescribed for ~~that~~ the day the powders in the single-dose packets were ingested. A flavor packet containing

powdered Crystal Light® Ice Tea was provided to each patient for use, as desired, with the ~~prep~~ single-dose packet to encourage drinking.

RESULTS:

[0025] The results reported ~~here~~ herein are representative of those obtained in the experimental group.

PATIENT #1:

[0026] ~~This is~~ The patient was a 61 year-old female with weight loss and decrease in appetite. She ~~underwent~~ consumed a clear liquid diet the day before ~~with bowel prep taken~~ ingesting the single-dose packets at 10 a.m. and at 4 p.m. ~~Good prep and~~ Satisfactory clean-out of the colon was observed by an adequate view of the colon and ~~was~~ verified ~~by~~ with multiple photographs taken during the colonoscopy. ~~She~~ The patient had no complaints of cramping or complaints of nausea. But the patient expressed a mild~~. Mild~~ dislike of the taste.

[0027] View of transverse colon of Patient #1 appears at Figure 1.

PATIENT #2:

[0028] ~~This is~~ The patient was an 86 year-old female with a history of anemia who ~~underwent bowel prep, taking it~~ used the disclosed method by taking a single-dose packet twice the day before examination along with a clear liquid diet. There was adequate bowel clean-out ~~and~~ to present a good view of the entire colon~~ with no~~ No abnormalities were found in the colon.

[0029] View of transverse colon of Patient #2 appears at Figure 2.

PATIENT #3:

[0030] ~~This is~~ The patient was a 62 year-old male with hemorrhoidal ~~bleed~~ bleeding and diarrhea before undergoing a colonoscopy. ~~Bowel prep~~ The single-dose packets were taken at 10 a.m. and 4 p.m. the day before the colonoscopy and a clear liquid diet ~~were~~ was prescribed. ~~He~~ The patient had no complaints of nausea, vomiting, or discomfort. The patient made no ~~No~~ complaints of taste abnormalities. ~~He was given~~ A flavor packet was given to the patient to use as needed.

[0031] View of sigmoid colon of Patient #3 appears at Figure 3.

PATIENT #4:

[0032] ~~This is~~ The patient was[[,]] a 74 year-old male with a history of colon polyps ~~for a surveillance colonoscopy, underwent~~. The patient used the disclosed method for bowel prep and bowel clean-out, along with one Dulcolax 10 milligram tablet at 10 a.m. and 4 p.m. the day before a surveillance colonoscopy. ~~using the dry prep disclosed method at 10 a.m. and 4 p.m. with one Dulcolax 10 milligram tablet.~~ Adequate bowel clean-out ~~showing~~ revealed diverticulosis ~~at~~ in the sigmoid colon. Mild rectal irritation and inflammation with a good view of the entire colon was ~~verified~~ recorded by ~~video~~ photographs taken during the colonoscopy. Tolerance of the ~~prep and~~ disclosed method was reported ~~and~~ with a slight complaint about taste~~, but no crampy~~. No cramping sensation was reported. The patient did not experience and

reported ~~No~~ no nausea and vomiting from using the bowel-clean out methods.~~, that he has had with other preps~~.

[0033] View of descending colon of Patient #4 appears at Figure 4.

PATIENT #5:

[0034] ~~This is~~ The patient was a 50 year-old female who underwent a surveillance colonoscopy because of ~~with~~ a first degree relative with colon cancer ~~who underwent surveillance colonoscopy~~. The patient ingested the single-dose packets ~~Took the bowel prep~~ at 10 a.m. and 4 p.m. the day before the surveillance colonoscopy ~~; some~~. Some stool was found in the sigmoid colon. There was no liquid~~, able~~. It was possible to suction out the colon completely ~~and got~~ to obtain a good visualization of the entire colon verified by ~~video~~ photographs taken during ~~he~~ the colonoscopy ~~with the patient having no~~. No complaints of product tolerance were made by the patient. No nausea ~~and~~, no vomiting, ~~with~~ no diarrhea, and no ~~crampy~~ cramping sensation were reported by the patient.

[0035] View of transverse colon of Patient #5 appears at Figure 5.

PATIENT #6:

[0036] ~~This is~~ The patient was a 50-year old female ~~who presented~~ with continuing diarrhea. ~~for~~ A colonoscopy was used to look for a possible cause of the diarrhea. The ~~bowel prep was~~ single-dose packets were taken at 10 a.m. and 4 p.m. ~~on~~ the day before the ~~exam,~~ colonoscopy, along with a clear liquid diet. The bowel clean-out ~~prep~~ was good~~, with~~ and provided an adequate view of colon.

[0037] View of transverse colon of Patient #6 appears at Figure 6.

[0038] While the foregoing invention has been disclosed according to its various embodiments, the disclosed invention shall be described according to the scope and meaning of the appended claims.